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Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery

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Abstract

Background. We assessed whether a near-infrared spectroscopy (NIRS)-based algorithm for the personalized optimization of cerebral oxygenation during cardiopulmonary bypass combined with a restrictive red cell transfusion threshold would reduce perioperative injury to the brain, heart, and kidneys.

Methods. In a randomized controlled trial, participants in three UK centres were randomized with concealed allocation to a NIRS (INVOS 5100; Medtronic Inc., Minneapolis, MN, USA)-based 'patient-specific' algorithm that included a restrictive red cell transfusion threshold (haematocrit 18%) or to a 'generic' non-NIRS-based algorithm (standard care). The NIRS algorithm aimed to maintain cerebral oxygenation at an absolute value of $>50\%$ or at $>70\%$ of baseline values. The primary outcome for the trial was cognitive function measured up to 3 months postsurgery.

Results. The analysis population comprised eligible randomized patients who underwent valve or combined valve surgery and coronary artery bypass grafts using cardiopulmonary bypass between December 2009 and January 2014 ($n=98$ patient-specific algorithm; $n=106$ generic algorithm). There was no difference between the groups for the three core cognitive domains (attention, verbal memory, and motor coordination) or for the non-core domains psychomotor speed and visuo-spatial skills. The NIRS group had higher scores for verbal fluency; mean difference 3.73 (95% confidence interval 1.50, 5.96). Red cell transfusions, biomarkers of brain, kidney, and myocardial injury, adverse events, and health-care costs were similar between the groups.

Conclusions. These results do not support the use of NIRS-based algorithms for the personalized optimization of cerebral oxygenation in adult cardiac surgery.

Clinical trial registration. http://www.controlled-trials.com, ISRCTN 23557269.

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Key words: cardiopulmonary bypass; cerebral oxygenation; cognitive dysfunction; spectroscopy, near-infrared

Editor's key points

- Personalized optimization of cerebral oxygen saturation during cardiac surgery may reduce perioperative neuronal injury.
- One manoeuvre for optimization is blood transfusion, which poses its own risks.
- The authors developed an optimization protocol involving a transfusion threshold of haematocrit 18%.
- Cognitive outcomes were similar with this protocol compared with a generic protocol (no near-infrared spectroscopy optimization, haematocrit threshold 23%).

Brain injury occurs in up to 40% of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), where it contributes to morbidity, mortality, and the increased use of healthcare resources.[1] This has been attributed in part to cerebral hypoperfusion and hypoxia caused by non-physiological blood flow during CPB, often in the presence of diseases that result in abnormal autoregulation.[2 3]

Near-infrared spectroscopy (NIRS) is a non-invasive method for the measurement of regional cerebral oxygenation and has been shown to reflect cerebral mixed venous oxygen saturations in cardiac surgery patients.[4] It has been hypothesized that personalized goal-directed interventions directed towards increasing regional brain oxygen saturation as measured by NIRS during CPB might lead to reductions in brain injury[4] or reductions in injury to other organs, including the heart and kidneys, as a consequence of improved overall perfusion.[5] It has also been postulated that NIRS might be used to personalize transfusion decisions, whereby red cell transfusions are used as one component of a patient-specific algorithm designed to optimize tissue oxygenation.[6]

To test these hypotheses and to address clinical uncertainty regarding the benefits of NIRS-based algorithms[7] reflected by variability in their use,[8] we performed a multicentre randomized controlled trial comparing a personalized goal-directed NIRS-based algorithm that incorporated a restrictive red cell transfusion threshold *vs* standard care in adult patients undergoing heart valve surgery with or without coronary artery bypass grafting (CABG). The primary outcome for the trial was cognitive function measured up to 3 months postsurgery. Secondary outcomes included biomarkers of brain, kidney, and myocardial injury, adverse events, and resource use.

Methods

Trial design and participants

The effects of patient-specific cerebral oxygenation monitoring as part of an algorithm to reduce red cell transfusion in patients having heart valve surgery (PASPORT) trial (registration ISRCTN 23557269 on February 27, 2009) was a parallel-group randomized controlled trial conducted at three cardiac surgery centres in the UK. Male and female adult patients undergoing open valve or combined CABG and open valve surgery were eligible. Exclusions, listed in Supplementary material Table S1, included patients with pre-existing neurological disease or inflammatory states. Participants provided written informed consent before surgery but became eligible for randomization only if they scored ≥24 on the Mini Mental State Examination (indicating no cognitive impairment). The allocated intervention was applied during CPB. Participants were followed up until discharge and at 6 weeks and 3 months after randomization. The trial complied with the Declaration of Helsinki. A UK National Health Service (NHS) Research Ethics Committee (REC) approved the study (09/H0102/13) on June 15, 2009. A detailed protocol has been reported elsewhere.[9] University Hospitals Bristol NHS Trust was the trial sponsor. Changes to the trial after commencement are described in the Supplementary material.

Randomization and blinding

Participants were randomly allocated to either the 'generic' or 'patient-specific' algorithms for optimizing tissue oxygenation during CPB in a 1:1 ratio, stratified by centre and surgical procedure (valve only or combined CABG and valve). Allocations, blocked with varying block sizes, were generated by computer and concealed using a secure password-protected internet-based randomization system. Randomization occurred before surgery after written informed consent was given and eligibility confirmed and as close to the planned surgery time as possible. Patients and outcome assessors were blinded to group allocation.

Interventions

The trial compared two algorithms for optimizing tissue oxygenation during CPB, generic and patient-specific algorithms. The interventions were defined as follows.

Generic algorithm (including a standard transfusion threshold)

This was a generic algorithm for optimizing tissue oxygenation based on global measures of oxygen utilization and including a predefined intraoperative haematocrit transfusion threshold of 23%.

Patient-specific algorithm (including a restrictive transfusion threshold)

This was a patient-specific, goal-directed algorithm based on the monitoring and optimization of regional cerebral oxygen saturation measured using the INVOS 5000 NIRS device (Somanetics, IN, USA), combined with a predefined 'restrictive' intraoperative haematocrit transfusion threshold of 18%. Optimization of cerebral oxygenation used a modified Murkin protocol[10] (see Supplementary Table S2) that aimed to maintain INVOS values at an absolute value of >50% or at >70% of baseline values obtained in the anaesthetic room before induction whilst breathing room air. If target cerebral oxygenation values were not achieved by modifying aspects of pump flow, gas exchange, or depth of anaesthesia as specified in the algorithm, red cells could be transfused above the 18% haematocrit threshold.

Details of perioperative care protocols, monitoring of protocol compliance, blinding of clinical staff, and other steps to mitigate bias are described in the Supplementary material.

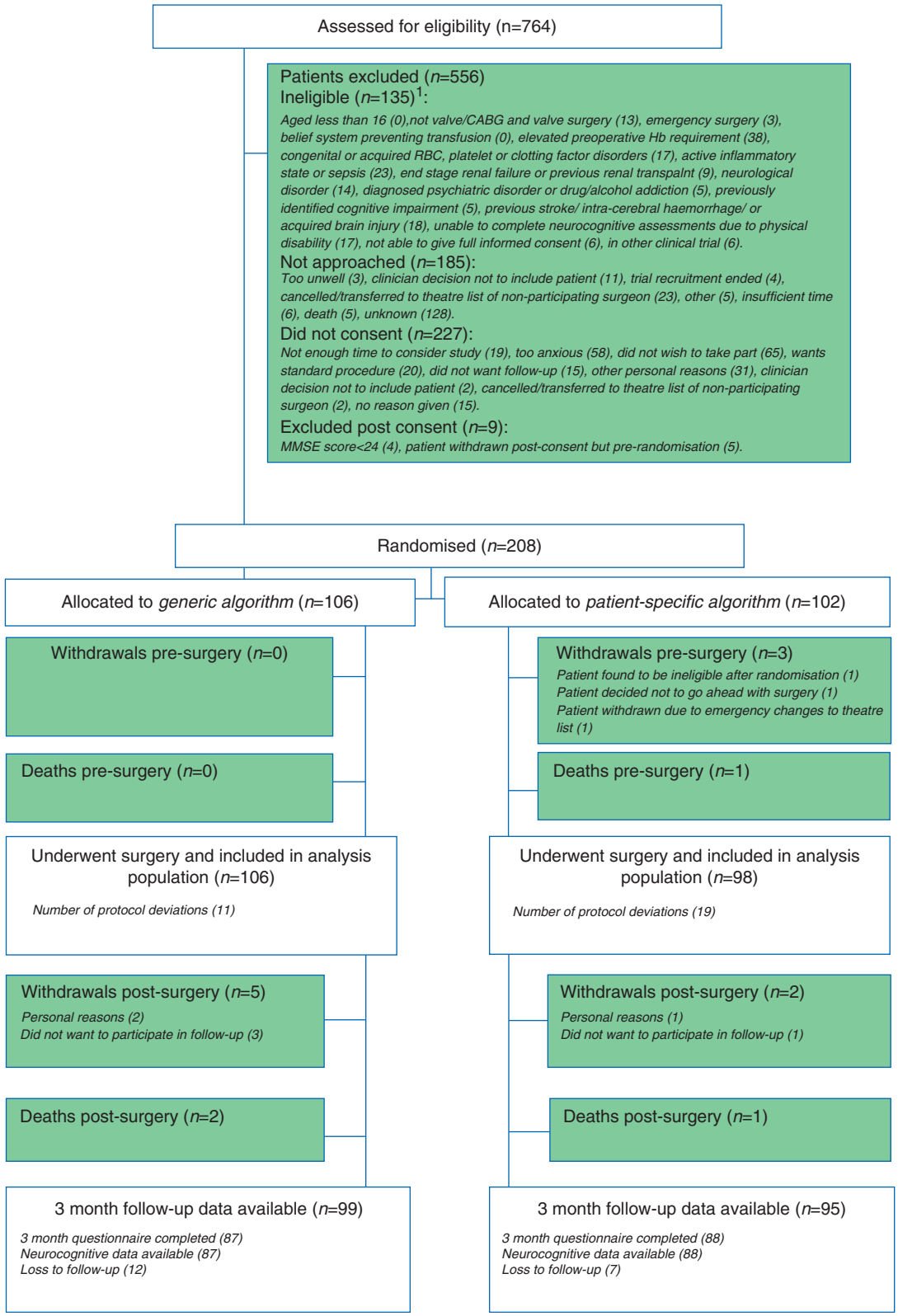

Fig 1 Flow of participants showing eligibility, recruitment, protocol deviations, withdrawals, and loss to follow-up in the PASPORT trial. MMSE, mini mental state examination.

Table 1 Participant characteristics and history. AF, atrial fibrillation; CCS, Canadian Cardiology Society; CVA, cerebrovascular accident; IQR, interquartile range; NYHA, New York Heart Association; TIA, transient ischaemic attack; WTAR, Wechsler test of adult reading. Missing data are as follows (generic algorithm, patient-specific algorithm): *one patient with missing data (0, 1); †one patient with missing data (0, 1); ‡15 patients with missing data (9, 6); ¶52 patients with missing data (29, 23); §seven patients with missing data (2, 5)

Characteristic		Randomized to generic algorithm (n=106)		Randomized to patient-specific algorithm (n=98)		Overall (n=204)	
		n	%	n	%	n	%
Demography							
Sex (female)		32/106	30	32/98	33	64/204	31
Age (yr; mean, range)		70.0	29.5–88.7	65.9	18.5–86.6	68.0	18.5–88.7
BMI (kg m^{-2}; mean, SD)		27.5	4.6	27.8	5.6	27.6	5.1
NYHA class	I	25/106	24	20/98	20	45/204	22
	II	50/106	47	43/98	44	93/204	46
	III	30/106	28	33/98	34	63/204	31
	IV	1/106	1	2/98	2	3/204	1
Canadian Cardiology Society class	Asymptomatic	49/106	46	53/98	54	102/204	50
	I	18/106	17	21/98	21	39/204	19
	II	21/106	20	15/98	15	36/204	18
	III	15/106	14	9/98	9	24/204	12
	IV	3/106	3	0/98	0	3/204	1
Angiogram/echocardiography results							
Left ventricular function	Good (>50%)	90/106	85	85/98	87	175/204	86
	Moderate (30–50%)	16/106	15	13/98	13	29/204	14
>50% disease in left main stem		2/106	2	0/98	0	2/204	1
Coronary disease, number of vessels*	None	71/106	67	70/97	72	141/203	6
	Single	15/106	14	11/97	11	26/203	13
	Double	11/106	10	9/97	9	20/203	10
	Triple	9/106	8	4/97	4	13/203	6
	Not investigated	0/106	0	3/97	3	3/203	1
Blood and urine results							
Haemoglobin, gdL^{-1} (median, IQR)		14.2	(13.1, 15.5)	14.7	(13.3, 16.2)	14.4	(13.2, 16.2)
Haematocrit, % (median, IQR)†		40.0	(37.7, 42.0)	41.0	(38.0, 43.0)	41.0	(38.0, 43.0)
Platelets, $\times 10^9$L^{-1} (median, IQR)		220.0	(192.0, 258.0)	212.0	(186.0, 252.0)	217.0	(186.5, 255.5)
Creatinine, umolL^{-1} (median, IQR)		92.0	(77.0, 105.0)	87.5	(77.0, 104.0)	90.0	(77.0, 105.0)
Urine output during 3 h, ml (median, IQR)‡		221.0	(144.0, 303.0)	250.0	(157.0, 370.5)	230.0	(152.0, 342.0)
Medical history							
Diabetes	No	100/106	94	86/98	88	186/204	91
	Diet	2/106	2	4/98	4	6/204	3
	Oral	4/106	4	6/98	6	10/204	5
	Insulin	0/106	0	2/98	2	2/204	1
Pacemaker	No	101/106	95	96/98	98	197/204	97
	Temporary	1/106	1	0/98	0	1/204	1
	Permanent	4/106	4	2/98	2	6/204	3
Heart rhythm	Sinus	82/106	77	76/98	78	158/204	77
	AF	21/106	20	19/98	19	40/204	20
	Block	1/106	1	1/98	1	2/204	1
	Paced	2/106	2	2/98	2	4/204	2
CVA or TIA		5/106	5	11/98	11	16/204	8
Smoking status	No	56/106	53	45/98	46	101/204	50
	Ex (>1 month)	43/106	41	47/98	48	90/204	44
	Yes	7/106	7	6/98	6	13/204	6
Previous cardiac surgery		6/106	6	5/98	5	11/204	5
Myocardial infarction		12/106	11	8/98	8	20/204	10
Operative priority	Elective	94/106	89	88/98	90	182/204	89
	Urgent	12/106	11	10/98	10	22/204	11
Additive EuroScore (median, IQR)		5	(4, 7)	5.0	(3, 6)	5.0	(4, 7)
Medications							
Heparin		2/106	2	0/98	0	2/204	1
Nitrates until theatre		1/106	1	0/98	0	1/204	1
Clexane within 12 h before surgery		1/106	1	1/98	1	2/204	1
Aspirin within 5 days before surgery		55/106	52	38/98	39	93/204	46
Clopidogrel within 5 days before surgery		3/106	3	3/98	3	6/204	3

Continued

Table 1 Continued

Characteristic	Randomized to generic algorithm (n=106)		Randomized to patient-specific algorithm (n=98)		Overall (n=204)	
	n	%	n	%	n	%
β-Blockers	52/106	49	37/98	38	89/204	44
Psychotic medications						
Hypnotics	4/106	4	1/98	1	5/204	2
Sedatives	4/106	4	1/98	1	5/204	2
Anxiolytics	4/106	4	0/98	0	4/204	2
Antidepressants	9/106	8	6/98	6	15/204	7
Any psychotic drug	17/106	16	8/98	8	25/204	12
Wechsler test of adult reading						
WTAR standard score (median, IQR)§	118.5	(108.0, 123.0)	117.0	(108.0, 122.0)	118.0	(108.0, 123.0)

Outcomes

Timings of outcome assessment are listed in Supplemental Table S3.

Primary outcome

The primary outcome for the trial was serial measures of cognitive function on or between 4 and 7 days after surgery and again at 3 months.[11 12] Cognitive function was assessed by qualified examiners, trained in the methods of neurocognitive assessment used in the study and blinded to treatment allocation before surgery. The following cognitive domains were tested.

- Attention: sustained and divided attention: trail-making test parts A and B.
- Verbal memory: Rey Auditory Verbal Learning Test.
- Visuo-spatial: block design from the Wechsler Adult Intelligence Scale.
- Psychomotor speed: digit symbol test from the Wechsler Adult Intelligence Scale–Revised test.
- Executive function/verbal fluency: controlled oral word association test.
- Motor coordination: grooved pegboard test, dominant and non-dominant hand.

To help interpret the cognitive function data, the following assessments were carried out for all participants.

- The Wechsler Test of Adult Reading (WTAR) provided a measure of intellectual ability, before surgery only.
- Documentation of medications known to interfere with neuropsychological functions was carried out before and after surgery.
- Assessment of the patient's current mental health was done using the General Health Questionnaire (GHQ-30) and Hospital Anxiety and Depression Scale (HADS) before and after surgery, to take into account the potential interaction between postoperative cognition and mood.

Secondary outcomes

Secondary outcomes included biomarkers of the inflammatory response [serum interleukin (IL)-6, IL-8], brain (serum S100), and myocardial (serum troponin) injury. The effects of optimization of cerebral oxygenation on kidney injury were assessed by measurement of serum creatinine and calculated creatinine clearance, and urine biomarkers of inflammation [neutrophil gelatinase associated lipocalcin (NGAL), liver-fatty acid binding protein (L-FAB)] and tubular epithelial injury [kidney injury molecule-1 and IL-18]. Clinical outcomes, resource use, and quality of life were also recorded (Supplementary Table S4).

Sample size

We estimated that a sample size of 75 participants per group would be sufficient to detect small-to-moderate standardized differences between the two groups of 0.33 for the primary outcome cognitive function (adjusting for baseline) and 0.4 for inflammation and organ injury biomarkers (adjusting for baseline and using four repeated measures) with 80% power and 5% significance (two tailed). Correlations between repeated measures were assumed to be 0.7. For time to cardiac intensive care unit or hospital discharge, the sample size allowed a hazard ratio (HR) of 1.65 to be detected. During the trial, at the request of the funder, the sample size was increased to 100 patients per group because of a higher than expected dropout rate and a lower than expected correlation between baseline and postintervention cognitive function (no comparison between groups was made when the sample size assumptions were reviewed).

Statistical analysis

The analysis population included all randomized participants, excluding patients who died or withdrew after randomization but before surgery. Outcomes are reported by intention to treat and were directed by a prespecified statistical analysis plan (see Supplementary material). Continuous variables are summarized using the mean (SD), or the median and interquartile range (IQR) if the distribution is skewed, and categorical data are summarized as a number and percentage. Near-infrared spectroscopy was summarized as an area under the curve (AUC), as described in detail in the Supplementary material. Primary and secondary outcomes were compared using linear mixed model (continuous variables measured at multiple time points), multiple (continuous variables summarized as a single measurement), logistic (binary variables), or Cox proportional hazards (time to event variables) regression, with the generic algorithm as the reference group. All analyses were adjusted for the stratification variables, centre, and surgical procedure. Treatment effect estimates are reported with 95% confidence intervals (CIs). Likelihood ratio tests were used to determine statistical significance, and two tailed P-values <0.05 were considered statistically significant. Neurocognitive outcomes were adjusted for the stratification variables and for reading ability at

Table 2 Cognitive function. CI, confidence interval; COWAT; Controlled Oral Word Association Test; GMR, geometric mean ratio; IQR, interquartile range; RAVLT, Rey Auditory Verbal Learning test; WAIS, Wechsler Adult Intelligence Scale; controlled oral word association test; WTAR; Wechsler Test of Adult Reading MD, mean difference; OR, odds ratio. Data summarized are scaled scores, not raw scores. All treatment estimates are reported with and without adjustment for medications, HADs and GHQ were measured after surgery. Raw data are expressed as the mean (SD), except trail-making and visual motor coordination, which are expressed as the median (IQR). Missing data are as follows (generic algorithm, patient-specific algorithm): *seven patients with missing data (0, 7); †35 patients with missing data (20, 15); ‡31 patients with missing data (20, 11); ¶19 patients with missing data (9, 10); §eight patients with missing data (1, 7); ‖41 patients with missing data (25, 16); #44 patients with missing data (25, 19); **34 patients with missing data (21, 13); ††nine patients with missing data (0, 9); ‡‡42 patients with missing data (23, 19); ¶¶34 patients with missing data (22, 12); §§18 patients with missing data (6, 12); ‖‖43 patients with missing data (23, 20); ##35 patients with missing data (22, 13); ***16 patients with missing data (5, 11); †††33 patients with missing data (20, 13)

Test		Randomized to generic algorithm (n=106)		Randomized to patient-specific algorithm (n=98)		Adjusted for baseline covariates		Adjusted for time-specific covariates	
		Mean	SD	Mean	SD	Effect (95% CI)	P-value	Effect (95% CI)	P-value
1. Attention: trail making (lower score is better)									
Trail B completion	Baseline*	98.5	(74.0, 140.0)	86.0	(62.0, 111.0)				
(s; median, IQR)	5 days postoperative†	104.5	(80.0, 159.0)	102.0	(76.0, 142.0)				
	3 months postoperative‡	87.0	(64.0, 126.0)	76.0	(60.0, 98.0)				
	Treatment×time interaction						0.329		0.166
	Overall					GMR=0.99 (0.93, 1.07)	0.882	GMR=0.99 (0.91, 1.06)	0.709
2. Verbal memory: RAVLT (higher score is better)									
Trial VI having	Baseline¶	90.8	17.5	96.2	17.0				
adjusted for age	5 days postoperative#	80.9	16.0	81.2	14.9				
	3 months postoperative**	92.6	17.1	93.9	14.8				
	Treatment×time interaction						0.534		0.832
	Overall					MD = −1.75 (−5.22, 1.72)	0.326	MD = −0.96 (−4.65, 2.74)	0.614
3. Visuo-spatial skills: WAIS III (Wechsler; higher score is better)									
Block design having	Baseline§	11.3	3.6	11.2	2.6				
adjusted for age	5 days postoperative‖	10.9	3.6	10.5	2.8				
	3 months postoperative**	12.0	3.5	11.6	3.0				
	Treatment×time interaction						0.815		0.961
	Overall					MD = −0.25 (−0.77, 0.28)	0.364	MD = −0.001 (−0.57, 0.57)	0.153
4. Psychomotor speed: WAIS III (Wechsler; higher score is better)									
Digital symbol coding	Baseline††	9.3	2.6	9.3	2.6				
having adjusted for	5 days postoperative‡‡	8.1	2.6	8.4	2.5				
age	3 months postoperative¶¶	10.4	2.8	10.4	2.7				
	Treatment×time interaction						0.624		0.961
	Overall					MD = 0.08 (−0.37, 0.52)	0.733	MD = 0.33 (−0.12, 0.79)	0.153
5. Executive function/verbal fluency: multilingual aphasia (COWAT; higher score is better)									
Word score having	Baseline§§	42.2	12.3	44.2	11.2				
adjusted for age and	5 days postoperative‖‖	37.1	12.9	42.6	13.7				
years of education	3 months postoperative##	41.6	10.5	45.6	14.1				
	Treatment×time interaction						0.428		0.141
	Overall					MD = 2.72 (0.64, 4.80)	0.01	MD = 3.73 (1.50, 5.96)	0.0011

Continued

Table 2 Continued

Test		Randomized to generic algorithm (n=106)		Randomized to patient-specific algorithm (n=98)		Adjusted for baseline covariates		Adjusted for time-specific covariates	
		Mean	SD	Mean	SD	Effect (95% CI)	P-value	Effect (95% CI)	P-value
6. Visual motor coordination: peg board (lower score is better)									
Peg board completion (s; median, IQR)	Baseline***	83.0	(71.0, 104.0)	77.0	(69.0, 102.0)				
	5 days postoperative#	97.0	(77.0, 120.0)	94.0	(78.0, 123.0)				
	3 months postoperative†††	83.5	(72.0, 100.0)	80.0	(70.0, 97.0)				
	Treatment×time interaction						0.412		0.608
	Overall					GMR=1.01 (0.97, 1.07)	0.533	GMR=0.99 (0.94, 1.04)	0.736

recruitment, medication, and preoperative GHQ-30, HADS-Anxiety and HADS-Depression scores. The overall treatment effect for the primary outcome and for other continuous outcomes measured at repeated time points was estimated across the postsurgery time points, with adjustment for baseline differences. Where there was a significant time×treatment interaction effect, estimates were calculated at each time point. Significant differences in either the overall effect or for individual time points were considered evidence of a treatment effect for that outcome. For the primary outcome, it was specified in the statistical analysis plan that four out of six domains significant at the 5% level would provide evidence to support the study hypotheses. The trial was not powered to detect differences in clinical outcomes, and their frequencies are tabulated descriptively.

All analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 13.0 (StataCorp LP, College Station, TX, USA).

Results

Trial cohort and patient flows

The flow of patients through the trial is shown in Fig. 1. Two hundred and eight patients were recruited and randomized between December 2009 and January 2014. Four patients withdrew before surgery. The analysis population therefore comprised 204 participants, 106 of whom were allocated to the generic algorithm and 98 to the patient-specific NIRS algorithm. Of the 204 randomized patients, 194 were eligible for follow-up at 3 months, and 175 completed the 3 month questionnaire and attended for the neurocognitive assessment, (n=87 generic algorithm, n=88 patient-specific algorithm). Details of patient withdrawals are listed in Supplementary Table S5. There were 30 protocol deviations; 11 in the generic algorithm group and 19 in the patient-specific algorithm group (Supplementary Table S6).

Participant characteristics

Baseline characteristics were similar in the two groups (Table 1). The mean age of participants was 68 (SD 11) yr, and 69% were male. The median EuroScore was 5 in both groups. Overall, 157 (77%) participants were listed for valve surgery and 47 (23%) for combined CABG and valve surgery. Bypass, cross-clamp, and the overall duration of the surgery were similar in the two groups (Supplementary Table S7). All participants were alive at the end of the surgery.

Primary outcome

The results of the neurocognitive tests are shown in Table 2. The scores for the cognitive domains attention, verbal memory, visuo-spatial skills, psychomotor speed, and visual motor coordination were similar between the groups. Effect estimates were not significantly altered by adjustment for medications and mental health during follow-up. For the executive function/verbal fluency domain, mean scores were significantly better in the patient-specific algorithm group [mean difference (MD)=2.72 (95% CI 0.64, 4.80)], which increased when accounting for medication and mental health both at baseline and during follow-up [MD = 3.73 (95% CI 1.50, 5.96)]. These differences did not meet the prespecified definition of a reduction in cognitive dysfunction.

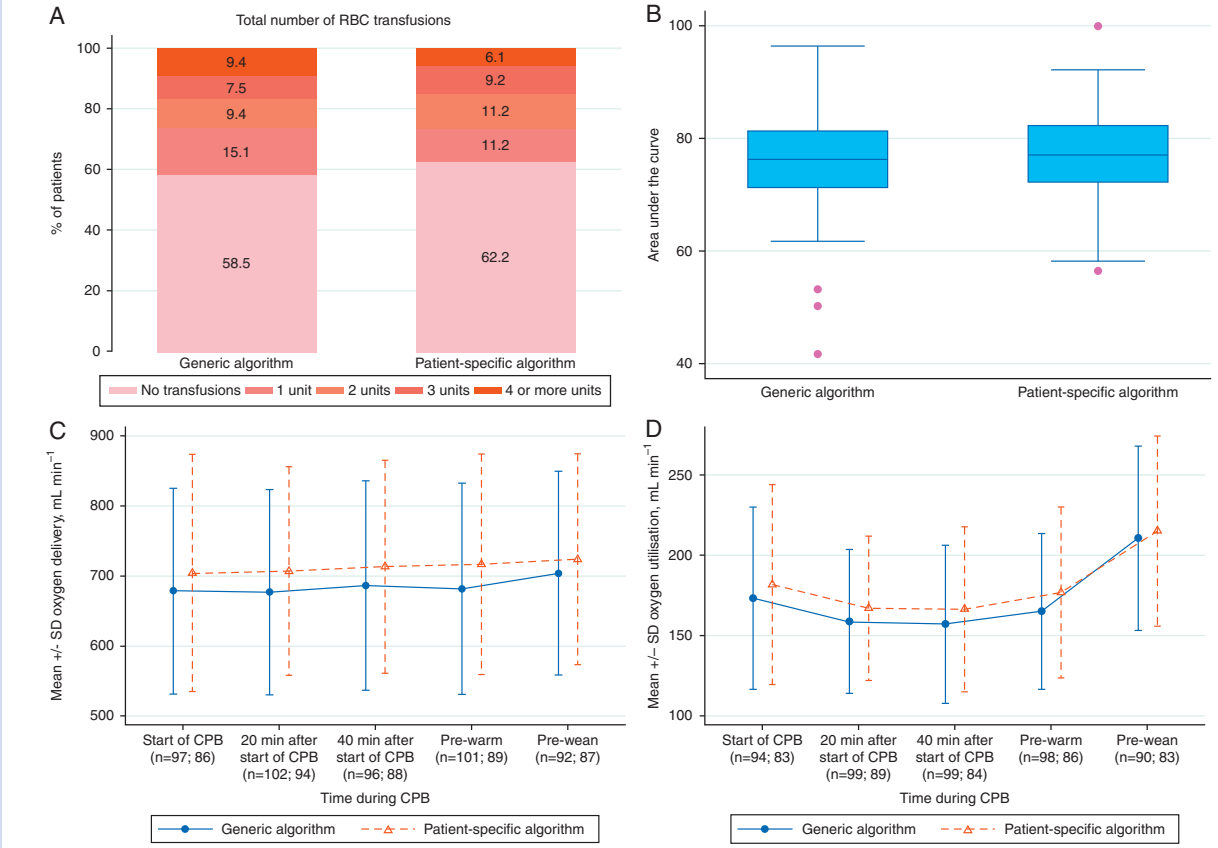

Fig 2 (A) Percentage of participants receiving RBC transfusions by group. (B) Cerebral oxygenation during the operative period expressed as mean NIRS area under the curve. (C) Mean oxygen delivery during CPB. (D) Oxygen utilization during CPB. Data are expressed as means (SD). CPB, cardiopulmonary bypass; NIRS, near-infrared spectroscopy; RBC, red blood cell.

Secondary outcomes

Results for the secondary outcomes are shown in Figs 2 and 3 and in Supplementary Table S8 and Figs S1 and S2. The groups were similar with respect to the frequency of red cell transfusion [RR=0.88 (0.63–1.23), P=0.47], NIRS area under curve, and mean oxygen delivery and consumption during cardiopulmonary bypass (CPB). Time to cardiac intensive care unit discharge [HR=1.15 (95% CI 0.87, 1.52), P=0.32], time to hospital discharge [HR = 1.10 (95% CI 0.83, 1.45), P=0.51], and quality of life measured using the EQ-5D [odds ratio=1.75 (95% CI 0.88, 3.50), P=0.11; Supplementary Table S9] were also similar. Serious expected adverse events and health-care costs to 3 months were similar between the groups (Supplementary Tables S10 and S11). Biomarker concentrations were similar in the two groups for inflammation (IL-6, IL-8), brain (serum S100), myocardial (serum troponin T), or kidney injury (Fig. 3 and Supplementary Fig. S2, Table S12 and Table S13).

Discussion

Main findings

The results of the PASPORT trial do not support the hypothesis that a patient-specific NIRS-based algorithm for the management of CPB results in reductions in neurocognitive dysfunction at up to 3 months postsurgery. Use of NIRS did not result in perioperative reductions in serum or urine biomarkers of brain, kidneys, and myocardial injury, or in resource use.

Strengths and limitations

The PASPORT trial compared a widely used patient-specific NIRS-based algorithm with standard care in three UK centres where this technology is in common use for the optimization of tissue oxygenation during CPB. It used detailed neurocognitive assessments and complementary clinical measures and biomarkers of injury and dysfunction in multiple organ systems.

The principal limitation of the trial was the limited blinding of health-care personnel; only the researchers responsible for the assessment of the neurocognitive and clinical outcomes and the laboratory staff carrying out the biomarker assays were blinded. We addressed this by documenting protocol compliance. This demonstrated that the nature of protocol non-adherence differed by group and also that the proportion of patients with non-adherence to the Murkin protocol in the intervention group was high (18%). This occurred despite all the members of the clinical team at each of the recruiting centres being familiar with the technology before conducting the trial.

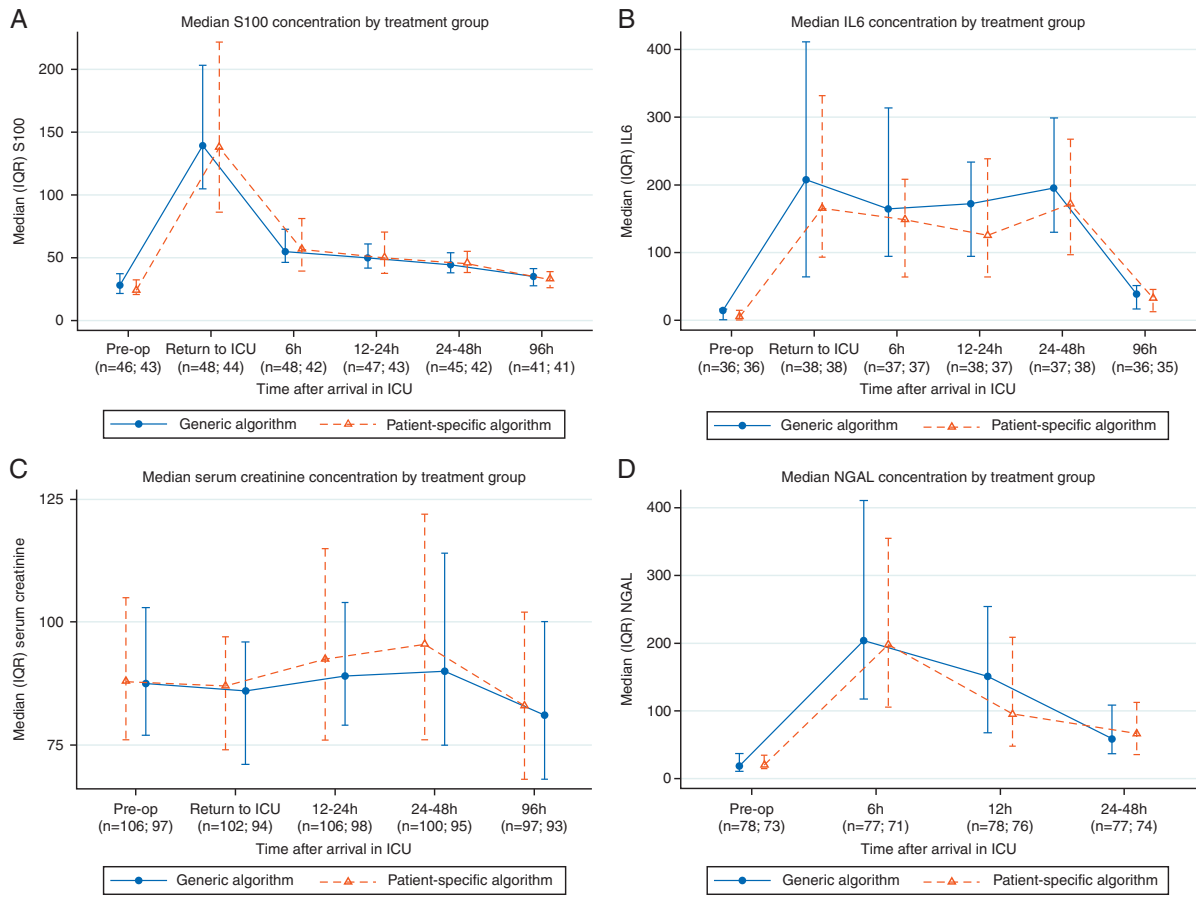

Fig 3 Serum biomarkers of inflammation and brain and kidney injury. (A) S100B, a marker of brain injury. (B) Serum IL-6, a marker of systemic inflammation. (C,D) Serum creatinine (C) and urinary NGAL (D), biomarkers of kidney injury. Data are presented as means (SD). ICU, intensive care unit; IL, interleukin; IQR, interquartile range; NGAL, neutrophil gelatinase-associated lipocalcin.

High levels of protocol non-adherence have been reported in a similar trial.[13] Although we cannot exclude the possibility that this may have introduced bias, it is equally possible that we have measured the normal application of this technology in a complex and highly variable operating theatre environment.

Another limitation is that the trial recruited throughout a prolonged period. It is possible that refinements in care may have occurred during this period, although as these changes will have been reflected in the trial cohort, this also increases the relevance of the findings to contemporary practice.

Clinical relevance

We detected a significant difference in one neurocognitive domain, executive function/verbal fluency, which favoured the patient-specific NIRS group. However, this is not a core domain as defined by the Consensus Statement for the Assessment of Neurocognitive function in Cardiac surgery,[11] and we did not conclude that this was sufficient to demonstrate efficacy. We also consider it unlikely that alternative definitions of neurocognitive dysfunction, such as the composite Z score, would have altered our findings. This conclusion was supported by no significant difference between the groups for the brain injury biomarker S100B. The NIRS levels were similar in both groups, with relatively few patients experiencing cerebral desaturation. We suggest that this may have contributed to our clinical findings; low frequencies of cerebral desaturation reduce the likelihood that NIRS-based algorithms will have clinical utility. This is perhaps attributable to the supranormal levels of oxygen delivery during CPB measured in the study; almost no patient had values approaching critical oxygen delivery ($<500\,ml\,min^{-1}$). Important risk factors for neurocognitive dysfunction, such as increased age, diabetes, or poor left ventricular function, were also uncommon, and this may have influenced our results. The potential for NIRS to contribute to cerebral protection will also have been influenced by the presence or absence of other factors that we did not quantify, such as cerebral emboli or pre-existing white matter changes.[14] Finally, our findings refuted the hypothesis that a patient-specific algorithm that aims to optimize cerebral NIRS values may have additional important benefits for other organs, such as the heart and kidneys.[5]

Conclusions

We did not demonstrate a clinical benefit for personalized, NIRS-directed management of patients during CPB.[4] These devices are in widespread use.[8] It is possible that our results are attributable to chance, although we detected no difference between NIRS and standard-care groups using multiple tests and assays that are sensitive markers of injury to a range of organ systems. Alternative hypotheses are that cerebral oxygen saturation measured by NIRS does not reflect cerebral oxygen utilization,[15] or that cerebral hypoxia is not the principal cause of post-CPB brain injury.[14] These findings support ongoing efforts to identify measures of cellular oxygen uptake[16] that may have clinical utility.

Authors' contributions

All of the study authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.
Conceived the trial: G.J.M. (chief investigator)
Wrote the application for funding (with others) and designed the trial: B.C.R., G.J.M., S.W., G.D.A., C.A.R.
Managed the conduct of the trial: L.E., B.C.R., C.A.R., G.J.M.
Principal investigators in Bristol and Hull: S.S., S.B., respectively
Managed the data during the trial and carried out the statistical analyses: G.C. under the supervision of C.A.R.
Supervised the administration of the intervention: R.D., E.N.
Analysis of health-care costs: E.A.S. under the supervision of S.W.
Drafted the report: C.A.R., G.C., B.C.R., G.J.M.
All authors reviewed the report for important intellectual content and approved the final version.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). S.B. declares that he has received payments from Covidien unrelated to the present work. The remaining authors declare that there are no conflicts of interest.

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